From good old biochemical analyses to high-throughput omics measurements and back

Heinemann, Matthias; Sauer, Uwe

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Editorial overview

Matthias Heinemann and Uwe Sauer

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Matthias Heinemann

University of Groningen, Molecular Systems Biology, Groningen Biomolecular Sciences and Biotechnology Institute, Nijenborgh 4, 9747 AG Groningen, Netherlands
e-mail: m.heinemann@rug.nl

Matthias Heinemann obtained a PhD in biochemical engineering from the RWTH Aachen University (Germany); did a postdoc with Sven Panke in the bioprocess lab of the ETH Zurich (Switzerland) followed by a group leader position at the Institute of Molecular Systems Biology at ETH Zurich (research unit of Uwe Sauer); since August 2009 he is professor for molecular systems biology at the University of Groningen (The Netherlands) leading a research program aiming at generating a system-level understanding of (microbial) metabolism.

Uwe Sauer

ETH Zurich, Switzerland
e-mail: sauer@imsb.biol.ethz.ch

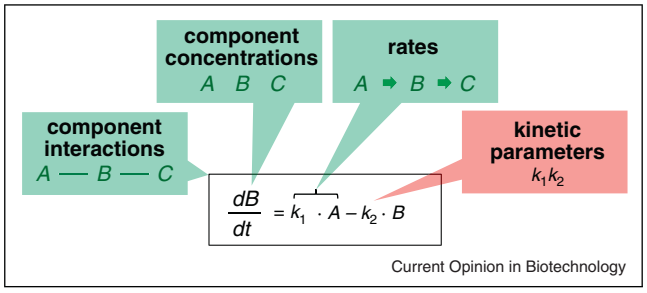
Uwe Sauer is professor of Systems Biology at the ETH Zurich (Switzerland) with a PhD in microbiology from the University of Göttingen (Germany). After a postdoc and junior group leader position with Jay Bailey (ETH Zurich) in metabolic engineering, his research focused on quantitative understanding of complex regulation processes that control cellular metabolism. His lab has pioneered the development of high-throughput methods for metabolomics and flux analysis.

Systems biology ultimately aims at generating quantitative understanding of how biological functions emerge from the interaction of molecular components [1,2]. Toward this challenge, biological experimentation using information-rich analytical methods must be combined with computational modeling [3]. In recent years, great advances were made in the development of analytical methods, which are still driving contemporary systems biology.

Most recent advances in analytical methods providing critical knowledge, insights and information necessary to build and test mathematical models of cellular systems are reviewed in this issue of *Current Opinions of Biotechnology*. The scope of the illustrated methods ranges from the population down to the single cell level, from measuring thousands of compounds to measuring binding characteristics of single biomolecular interactions, and from cell-averaging methods to methods measuring at high spatial resolution. Since certain measures cannot be directly quantified, also computational methods are being reviewed that allow inferring of non-measurable quantities from measurable quantities.

The covered analytical methods can be grouped into three classes. The first class attempts to quantify *cellular components and their modifications*. Here, five expert reviews comment on the most recent developments in comprehensive transcriptomics and proteomics, post-translational protein modifications, and metabolomics at the population and single cell level. Obviously, biological function can only emerge when these and other components of cellular systems interact with each other. Thus, the second class of methods focuses on *identifying, quantifying and monitoring component interactions*. These methods range from large-scale genetic interactions to transcriptional interactions in single cells and single-molecule approaches to characterize kinetics of biomolecular interactions. Three of these reviews elaborate on the rapidly developing field of protein–protein interaction analyses with foci on different methods. This topic is complemented by an article addressing the pivotal question how component interactions can be computationally inferred from large data sets. The third class of analytical methods focuses on *quantifying rates*, constituting an important class of biochemical measures that cannot be measured directly. Instead, computational models of various complexities are used to infer the desired rates from often very ingenious measurements. Conceptually simple models are required to quantify growth rates and molecule diffusion rates or organelle turnover rates, while quantification of metabolic and signaling rates require progressively more elaborate modeling approaches, and eventually estimating true signaling rates might not even be possible, as argued by Schaber and Klipp in this issue.

Figure 1



The green boxes denote three types of insights that are generated from measurement techniques reviewed in this issue and that are needed to ultimately build mechanistic models (white box): component interactions lay the basis for a model; component quantities and rates are required to determine model structure and kinetic parameters. The field of dedicated kinetic parameter assessment (red box) is lagging behind.

Obviously, not all relevant areas of analytical methods could be covered. Missing is, for example, current work on protein–DNA interactions. Also, the entire field of the crucially important image-based analyses was left out because it was covered in a recent focused issue [4]. Although much development is still necessary in these and the above mentioned three classes of analytical methods, we are convinced that the analytical community will ultimately achieve a satisfactory resolution at the level of space, time, and single cells. In contrast, we feel that one area — the area of protein–metabolite interactions — does not receive sufficient attention by the analytical community. Here, we mostly still rely on allosteric interactions we learned from decades of biochemical research, but there has been very little progress toward methods that would identify these interactions systematically and at a larger scope. In fact, the very recent paper by the Synder lab, where interactions between metabolites in the ergosterol pathway of yeast with the involved enzymes were systematically mapped out raises hopes that this somewhat neglected area will soon develop [5].

Overall, the three categories of measurements that we covered in this issue are required to build mechanistic models about biological systems: identified components and interactions between them establish the basis for each model, while component concentrations and rates are crucial to identify the right model structures and to estimate the unknown kinetic parameters (see Figure 1).

Realizing that kinetic parameters need to be estimated from measurement data (because they are largely unknown) leads us to the question whether or not a fourth category of measurement techniques is missing, that is the area of experimental determination of kinetic parameters, that is the *k*-values in the equation shown in Figure 1. Traditionally, these values were determined with good-old, extremely time-consuming biochemistry and it is clear that this approach is not suitable in a systems biology context where one inherently looks at larger and more complex systems. What can be done? Either these values are estimated from the other experimental data by means of parameter estimation to obtain *in vivo* kinetic constants, or the analytical biotechnology field tackles the immense problem of *in vitro* high-throughput biochemistry. Steps required toward this goal will likely involve the availability of suitable microtechnology and the ability to mimic *in vivo* conditions in such *in vitro* experiments. The latter has been demonstrated in a *tour de force* of traditional biochemistry by determining the kinetic constants of most glycolytic enzymes in yeast under *in vivo*-like conditions [6]. Initial steps toward a suitable microtechnology are reviewed in this issue by Maerkl — an approach that could potentially be exploited also for the determination of kinetic constants.

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